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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
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 NEWS  3  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS  4  MAY 10   CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS  5  MAY 11   KOREAPAT updates resume
 NEWS  6  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS  7  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS  8  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC
 NEWS 10  JUN 26   TULSA/TULSA2 reloaded and enhanced with new search and
                   and display fields
 NEWS 11  JUN 28   Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11   CHEMSAFE reloaded and enhanced
 NEWS 13  JUl 14   FSTA enhanced with Japanese patents
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 NEWS 15  AUG 09   INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28   ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30   CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11   CA/CAplus enhanced with more pre-1907 records
 NEWS 19  SEP 21   CA/CAplus fields enhanced with simultaneous left and right
                   truncation

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               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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FILE 'HOME' ENTERED AT 12:35:05 ON 21 SEP 2006

=>  file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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FULL ESTIMATED COST 0.21 0.21

FILE 'MEDLINE' ENTERED AT 12:35:19 ON 21 SEP 2006

FILE LAST UPDATED: 20 Sep 2006 (20060920/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s (proline or glycine) (L) (osteoarthritis or "rheumatoid arthritis" or
osteochondorosis or synovitis or osteoarthropathia or psoriatica)
         30538 PROLINE
         45378 GLYCINE
         30624 OSTEOARTHRITIS
         84970 "RHEUMATOID"
        116818 "ARTHRITIS"
         51221 "RHEUMATOID ARTHRITIS"
                 ("RHEUMATOID"(W)"ARTHRITIS")
             1 OSTEOCHONDOROSIS
          7696 SYNOVITIS
            39 OSTEOARTHROPATHIA
            86 PSORIATICA
L1           129 (PROLINE OR GLYCINE) (L) (OSTEOARTHRITIS OR "RHEUMATOID ARTHRITI
                 S" OR OSTEOCHONDOROSIS OR SYNOVITIS OR OSTEOARTHROPATHIA OR
                 PSORIATICA)

=> s l1 and (treatment or method)
       1933428 TREATMENT
        891042 METHOD
L2           30 L1 AND (TREATMENT OR METHOD)

=> d 1-30 bib abs

L2   ANSWER 1 OF 30     MEDLINE on STN
AN   2006460333     IN-PROCESS
DN   PubMed ID: 16882596
TI   Effects of low-intensity ultrasound (LIUS) stimulation on human cartilage
     explants.
AU   Min B-H; Woo J-I; Cho H-S; Choi B H; Park S-J; Choi M J; Park S R
CS   Departments of Orthopaedic Surgery.
SO   Scandinavian journal of rheumatology, (2006 Jul-Aug) Vol. 35, No. 4, pp.
     305-11.
     Journal code: 0321213. ISSN: 0300-9742.
CY   Norway
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ED   Entered STN: 3 Aug 2006
     Last Updated on STN: 3 Aug 2006
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AB Objective: To evaluate the effects of low-intensity ultrasound (LIUS) stimulation on the anabolic state of human cartilage from patients with osteoarthritis (OA).Methods: Explant cultures of human OA cartilage were stimulated for 10 min every day for 7 consecutive days using continuous-wave sonication at a frequency of 1 MHz with spatial and temporal average intensities of 0 (control), 40, 200, 500, or 700 mW/cm2. The effects of LIUS on cell proliferation were evaluated by 3H-thymidine incorporation. Proteoglycan synthesis was evaluated by the incorporation of 35S-sulfate and by Safaranin O staining. Collagen synthesis was evaluated by 3H-proline incorporation and immunohistochemistry.Results: At an intensity of 200 mW/cm2, LIUS treatment induced the expression of collagen type II and proteoglycan measured by the incorporation of radioactivity and specific staining of the cartilage explants. However, the expression decreased again at the higher intensities of 500 or 700 mW/cm2. Ultrasound had no stimulatory effect on cell proliferation at any intensity.Conclusion: LIUS has anabolic effects on human cartilage in explant cultures, indicating a potentially important method for the repair of osteoarthritic cartilage.

L2 ANSWER 2 OF 30 MEDLINE on STN
AN 2005255983 MEDLINE
DN PubMed ID: 15896432
TI Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial.
AU Marcora Samuele; Lemmey Andrew; Maddison Peter
CS School of Sport, Health and Exercise Sciences, University of Wales-Bangor, George Building, Holyhead Road, Bangor, Gwynedd LL57 2PX, UK.. s.m.marcora@bangor.ac.uk
SO Clinical nutrition (Edinburgh, Scotland), (2005 Jun) Vol. 24, No. 3, pp. 442-54. Electronic Publication: 2005-04-21.
Journal code: 8309603. ISSN: 0261-5614.
CY England: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200509
ED Entered STN: 18 May 2005
Last Updated on STN: 23 Sep 2005
Entered Medline: 22 Sep 2005
AB BACKGROUND & AIMS: Rheumatoid arthritis (RA) is complicated by cytokine-driven alterations in protein and energy metabolism and consequent muscle wasting (cachexia). The aim of this randomised controlled trial was to investigate the efficacy of a mixture of beta-hydroxy-beta-methylbutyrate, glutamine and arginine (HMB/GLN/ARG) as nutritional treatment for rheumatoid cachexia. METHODS: Forty RA patients supplemented their diet with either HMB/GLN/ARG or a nitrogen (7.19 g/day) and calorie (180 kcal/day) balanced mixture of alanine, glutamic acid, glycine, and serine (placebo) for 12 weeks. Body composition and other outcomes were assessed at baseline and follow-up, and analysed by mixed ANOVA. RESULTS: Dietary supplementation with HMB/GLN/ARG was not superior to placebo in the treatment of rheumatoid cachexia (groupxtime interactions $P>0.05$ for all outcomes). Both amino acid mixtures significantly increased (main effect of time) fat-free mass (727+/-1186 g, $P<0.01$), total body protein (719+/-1703 g, $P=0.02$), arms (112+/-183 g, $P<0.01$) and legs (283+/-534 g, $P<0.01$) lean mass, and some measures of physical function. No significant adverse event occurred during the study, but patients in the HMB/GLN/ARG group reported fewer gastrointestinal complaints compared to placebo. CONCLUSIONS: Dietary supplementation with HMB/GLN/ARG is better tolerated but not more effective in reversing cachexia in RA patients compared to the mixture of other non-essential amino acids used as placebo. Further

controlled studies are necessary to confirm the beneficial anabolic and functional effects of increased nitrogen intake in this population.

L2 ANSWER 3 OF 30 MEDLINE on STN
AN 2004605603 MEDLINE
DN PubMed ID: 15578912
TI Extracellular tropomyosin: a novel common pathway target for anti-angiogenic therapy.
AU Donate Fernando; McCrae Keith; Shaw David E; Mazar Andrew P
CS Attenuon, LLC, San Diego, CA 92121, USA.
SO Current cancer drug targets, (2004 Nov) Vol. 4, No. 7, pp. 543-53. Ref: 66
Journal code: 101094211. ISSN: 1568-0096.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200503
ED Entered STN: 7 Dec 2004
Last Updated on STN: 30 Mar 2005
Entered Medline: 29 Mar 2005
AB Angiogenesis is characterized by the development of new vasculature from pre-existing vessels and plays a central role in physiological processes such as embryogenesis, wound healing and female reproductive function, as well as pathophysiologic events including cancer, rheumatoid arthritis and diabetic retinopathy. The growth and metastasis of tumors is critically dependent upon angiogenesis. Although targeting angiogenesis as a therapeutic strategy has to date met with limited success in the clinic, the recent FDA approval of the anti-VEGF antibody Avastin has validated the use of anti-angiogenic therapeutic strategies for cancer treatment. We have recently identified several plasma proteins having anti-angiogenic properties, including Histidine-Proline-Rich Glycoprotein (HPRG) and activated high-molecular-weight kininogen (HKa). Both of these proteins are able to induce apoptosis in endothelial cells in vitro and can inhibit angiogenesis in vivo. Recent studies from our laboratories have also identified a novel cell-surface binding protein for HKa that mediates its anti-angiogenic activity. This protein, tropomyosin, is normally found inside the cell and is associated with the actin cytoskeleton, where it plays a critical role in stabilizing actin filaments in a variety of cell types. However, in angiogenic endothelial cells, tropomyosin appears to have extracellular localization. Previous studies have also suggested the involvement of tropomyosin in the anti-angiogenic activity of endostatin, and our recent work indicates that tropomyosin may mediate the antiangiogenic activity of HPRG as well. In this review, we summarize data describing extracellular tropomyosin as a novel receptor for multiple anti-angiogenic proteins. Extracellular tropomyosin may therefore represent a previously undescribed central target for the development of anti-angiogenic therapy.

L2 ANSWER 4 OF 30 MEDLINE on STN
AN 2004303116 MEDLINE
DN PubMed ID: 15203037
TI Liquid chromatography analysis of N-(2-mercaptopropionyl)-glycine in biological samples by ThioGlo 3 derivatization.
AU Penugonda Suman; Wu Wei; Mare Suneetha; Ercal Nuran
CS Department of Chemistry, University of Missouri-Rolla, 1870 Miner Circle, Rolla, MO 65409, USA.
SO Journal of chromatography. B, Analytical technologies in the biomedical and life sciences, (2004 Aug 5) Vol. 807, No. 2, pp. 251-6.
Journal code: 101139554. ISSN: 1570-0232.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 200501
ED Entered STN: 24 Jun 2004
Last Updated on STN: 19 Jan 2005
Entered Medline: 18 Jan 2005
AB N-(2-Mercaptopropionyl)-glycine (MPG) is a synthetic aminothiol antioxidant that is used in the treatment of cystinuria, rheumatoid arthritis, liver and skin disorders. Recent studies have shown that MPG can function as a chelating, cardioprotecting and a radioprotecting agent. Several other studies have shown that it may also act as a free radical scavenger because of its thiol group. Thiol-containing compounds have been detected in biological samples by various analytical methods such as spectrophotometric and colorimetric methods. However, these methods require several milliliters of a sample, time-consuming procedures and complicated derivatization steps, as well as having high detection limits. The present study describes a rapid, sensitive and relatively simple method for detecting MPG in biological tissues by using reverse-phase HPLC. With ThioGlo 3 [3H-Naphto[2,1-b] pyran, 9-acetoxy-2-(4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl) phenyl-3-oxo-)] as the reagent, highly fluorescent derivatives of thiols can be obtained that are suitable for HPLC. MPG is derivatized with ThioGlo 3 and is then detected flourimetrically by reverse phase HPLC using a C18 column as the stationary phase. Acetonitrile: Water (75:25) with acetic acid and phosphoric acid (1 mL/L) is used as the mobile phase (excitation wavelength, 365 nm; emission wavelength, 445 nm). The calibration curve for MPG is linear over a range of 10-2500 nM (r=0.999) and the coefficients of the variation of within-run and between-run precision were found to be 0.3 and 2.1%, respectively. The detection limit was 5.07 nM per 20 microL injection volume. Quantitative relative recovery of MPG in the biological samples (plasma, lung, liver, kidney and brain) ranged from 90+/-5.3 to 106.7+/-9.3 %. Based on these results, we have concluded that this method is suitable for determining MPG in biological samples.

L2 ANSWER 5 OF 30 MEDLINE on STN
AN 2003505928 MEDLINE
DN PubMed ID: 14583567
TI Beta irradiation decreases collagen type II synthesis and increases nitric oxide production and cell death in articular chondrocytes.
AU Ailland J; Kampen W U; Schunke M; Trentmann J; Kurz B
CS Institute of Anatomy, University of Kiel, Olshausenstr 40, D-24098 Kiel, Germany.
SO Annals of the rheumatic diseases, (2003 Nov) Vol. 62, No. 11, pp. 1054-60. Journal code: 0372355. ISSN: 0003-4967.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200312
ED Entered STN: 30 Oct 2003
Last Updated on STN: 16 Dec 2003
Entered Medline: 15 Dec 2003
AB BACKGROUND: When synovitis is proved, intra-articularly injected beta emitting radionuclides like yttrium-90 ((90)Y) are used to treat the inflamed synovium. OBJECTIVE: To study the viability, matrix production, and NO production during or after (90)Y treatment of chondrocytes. METHODS: Monolayer, alginate, and explant cultures of primary bovine articular chondrocytes as well as synoviocytes were incubated with 0-3 MBq (90)Y/ml medium for four days from culture day 3 onwards. Cell viability was demonstrated by light and electron microscopy or by trypan blue or ethidium bromide/fluorescein diacetate staining, membrane integrity by measurement of lactate dehydrogenase (LDH) activity in the culture supernatants. Biosynthetic activity was demonstrated by incorporation of [(3)H]proline and immunocytochemical staining of collagen type II. NO production was measured with the Griess reagent.

RESULTS: In chondrocyte and synoviocyte monolayer cultures radiation caused a dose dependent increase in cell death and membrane destruction within four days. In alginate and explant cultures, where proliferation is low, no significantly increased LDH activity was seen, and cell viability was approximately 100% for up to 14 days after irradiation. Collagen type II expression (alginate) and biosynthetic activity (alginate and explants) were decreased dose dependently while there was an increase in NO production. Light and electron microscopy data showed that five weeks after irradiation all cells in alginate and most cells in explants subjected to 3 MBq (90)Y/ml were dead, whereas after lower amounts of irradiation several morphologically intact cells were found. CONCLUSIONS: beta Irradiation may influence the long term maintenance of cartilage tissue or the aetiology of degenerative joint diseases.

L2 ANSWER 6 OF 30 MEDLINE on STN
AN 2003111291 MEDLINE
DN PubMed ID: 12623287
TI Malondialdehyde oxidation of cartilage collagen by chondrocytes.
AU Tiku M L; Allison G T; Naik Karishma; Karry S K
CS Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ 08903-0019, USA.. tikuml@umdnj.edu
SO Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, (2003 Mar) Vol. 11, No. 3, pp. 159-66.
Journal code: 9305697. ISSN: 1063-4584.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 8 Mar 2003
Last Updated on STN: 8 Jun 2003
Entered Medline: 6 Jun 2003
AB OBJECTIVE: The damage to cartilage collagen is a central event in the pathogenesis of cartilage aging and osteoarthritis (OA). We have previously developed an in vitro model of cartilage degradation which shows that chondrocyte-dependent lipid peroxidation mediates cartilage collagen degradation. The goal of our study was to investigate the role of vitamin C in this degradation model and to investigate effect of chondrocyte-dependent lipid peroxidation in the oxidation of cartilage collagen. METHODS: We studied primary articular chondrocytes. Effect of vitamin C was investigated in the previously described model. Serum-free stimulated and unstimulated chondrocyte-matrix extracts were subjected to SDS-PAGE and immunoblot analysis. Malondialdehyde (MDA)-protein oxidation of cartilage proteins was demonstrated by the reactivity of chondrocyte extracts to a monoclonal antibody, MDA2, which detects MDA-lysine adducts. RESULTS: Vitamin C treatment of chondrocyte cultures resulted in significant enhanced incorporation of 3H-proline label in cell-matrix. Cells treated with vitamin C, as compared to control untreated cells showed decreased spontaneous release of labeled matrix. Vitamin C treated or not treated chondrocytes responded comparably to stimulation with the agonist calcium ionophore A23187. The serum-free in vitro culture of chondrocytes resulted in MDA-protein oxidation. The treatment of chondrocytes with A23187 resulted in the enhancement of MDA-protein oxidation. The immunoblot reactivity pattern of extracts to MDA2 antibody and to polyclonal anti-type II collagen antibody was somewhat similar, which suggests that these two different types of antisera exhibit a crossreaction to chondrocyte proteins. Chondrocyte extracts were pretreated both with and without pure collagenase, and then subjected to immunoblot analysis. Only collagenase treated extracts showed a disappearance, or significant reduction, of larger than 60 kDa size MDA2 immunoreactive proteins. This suggests that the proteins that disappeared after the enzyme treatment were collagen proteins and which had also been modified by MDA oxidation. CONCLUSIONS: These observations suggest that collagen hydroxylation of matrix by vitamin C

does not play a role in this model of chondrocyte-dependent collagen degradation. Also, this study demonstrates that chondrocyte-derived lipid peroxidation product MDA mediates oxidation of cartilage collagens. Oxidative modification of cartilage collagen in vivo could result in alteration of biochemical and biophysical properties of cartilage collagen fibrils, making them prone to degradation, thus initiating the changes observed in aging and OA.

L2 ANSWER 7 OF 30 MEDLINE on STN
AN 2003103974 MEDLINE
DN PubMed ID: 12595626
TI Urinary levels of creatine and other metabolites in the assessment of polymyositis and dermatomyositis.
AU Chung Y-L; Wassif W S; Bell J D; Hurley M; Scott D L
CS Department of Medicine, King's College School of Medicine and Dentistry, Bessemer Road, Denmark Hill, London SE5 9PJ, UK.. ychung@sghms.ac.uk
SO Rheumatology (Oxford, England), (2003 Feb) Vol. 42, No. 2, pp. 298-303. Journal code: 100883501. ISSN: 1462-0324.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200305
ED Entered STN: 6 Mar 2003
Last Updated on STN: 13 May 2003
Entered Medline: 9 May 2003
AB BACKGROUND: A simple and reliable method is needed to assess disease activity and monitor the efficacy of therapy in polymyositis (PM) and dermatomyositis (DM). This study used in vitro proton ((1)H) magnetic resonance spectroscopy (MRS) to explore whether excretion of urinary metabolites can be used as a reliable marker of disease in PM and DM patients. METHODS: Urine samples were obtained from PM/DM patients (n=34), healthy controls (50) and subjects with known muscle-wasting conditions including adult-onset muscular dystrophy (8), stroke patients (10), rheumatoid arthritis (RA) patients on steroids (13) and not on steroids (16) and patients with alcoholic myopathy (12). Levels of urinary metabolites were then correlated with creatine kinase (CK) activities and quadriceps muscle strength. RESULTS: Creatine was detected in the urine in 26 of 35 patients with PM/DM, four of 60 cases with other medical disorders (including one with adult-onset dystrophy, one with a stroke and two with RA who were not on steroids) and 10 of 50 healthy controls. The urinary creatine/creatinine ratio exceeded 0.4 in 20 patients with PM/DM but no patients with other medical disorders and no healthy controls. These differences were highly significant ($P<0.001$) by Kruskal-Wallis test (comparing all groups) and by Mann-Whitney U-tests (comparing individual groups with PM/DM cases). Citrate, glycine , choline-containing compounds and taurine levels were significantly increased in PM/DM when compared with controls. There were positive correlations between CK activities and choline-containing compounds ($r=0.78$, $P=0.0006$) and also between CK activities and betaine ($r=0.57$, $P=0.026$). CONCLUSIONS: This study shows significant differences in the urinary levels of creatine, choline-containing metabolites, betaine and citrate in PM/DM subjects compared with controls, although further work is required to elucidate the underlying metabolic processes.

L2 ANSWER 8 OF 30 MEDLINE on STN
AN 2002387916 MEDLINE
DN PubMed ID: 12048292
TI Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis.
AU van Ede A E; Laan R F J M; Blom H J; Boers G H J; Haagsma C J; Thomas C M G; De Boo T M; van de Putte L B A
CS Department of Rheumatology, University Medical Center St Radboud, Nijmegen, The Netherlands.
SO Rheumatology (Oxford, England), (2002 Jun) Vol. 41, No. 6, pp. 658-65.

Journal code: 100883501. ISSN: 1462-0324.
CY England: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200208
ED Entered STN: 25 Jul 2002
Last Updated on STN: 4 Mar 2003
Entered Medline: 8 Aug 2002
AB OBJECTIVE: To study (i) the influence of methotrexate (MTX) therapy on homocysteine and folate metabolism in patients with rheumatoid arthritis (RA), (ii) the influence of the C677T mutation in the methylenetetrahydrofolate reductase gene (MTHFR) on the change in plasma homocysteine levels during MTX treatment, and (iii) the interference of folate and homocysteine metabolism with the efficacy and toxicity of treatment with MTX. METHODS: The 113 patients enrolled in this study were participating in a 48-week, multicentre, double-blind, placebo-controlled study comparing the efficacy and toxicity of MTX treatment with and without folic or folinic acid supplementation. The MTX dose was 7.5 mg/week initially and increased to a maximum of 25 mg/week if necessary. Concentrations of total folate, 5-methyl tetrahydrofolate (in serum and in erythrocytes) and of homocysteine, cysteine and cysteine-glycine and the MTHFR genotype were determined before the start of the study, after 6 weeks, and after 48 weeks or on withdrawal from the study. Blood was drawn from fasting patients at a standardized time in the morning, 16 h after intake of MTX. The laboratory results were related to parameters of efficacy and toxicity of MTX treatment. RESULTS: Baseline values were distributed equally in the three treatment groups. The mean plasma homocysteine level (normal range 6-15 micromol/l) before the start of MTX was relatively high in all groups: 15.4 micromol/l [95% confidence interval (CI) 13.5 to 17.2] in the MTX plus placebo group (n=39), 14.3 micromol/l (95% CI 12.2 to 16.4) in the MTX plus folic acid group (n=35) and 15.9 micromol/l (95% CI 13.7 to 18.1) in the MTX plus folinic acid group (n=39). After 48 weeks of MTX therapy, the mean homocysteine level showed an increase in the placebo group (+3.6 micromol/l, 95% CI 1.7 to 5.6). In contrast, a decrease was observed in the groups supplemented with folic or folinic acid (folic acid, -2.7 micromol/l, 95% CI -1.4 to -4.0; folinic acid, -1.6 micromol/l, 95% CI -0.1 to -3.0). The differences in the change in plasma homocysteine level between the placebo group and each of the two folate-supplemented groups were statistically significant ($P<0.0001$), contrary to the difference between the folic and folinic acid groups ($P=0.26$). Linear regression analysis showed that the change in plasma homocysteine level was statistically significantly associated with folic or folinic acid supplementation ($P=0.0001$) but not with the presence or absence of the C677T mutation in the MTHFR gene. Homozygous mutants had a higher plasma homocysteine concentration at baseline. No relationship was found between the change in disease activity and the change in homocysteine concentration or the mean homocysteine concentration after 48 weeks of MTX therapy. Toxicity-related discontinuation of MTX treatment was not associated with the change in homocysteine concentration. CONCLUSIONS: Low-dose MTX treatment in RA patients leads to an increased plasma homocysteine level. Concomitant folate supplementation with either folic or folinic acid decreases the plasma homocysteine level and consequently protects against potential cardiovascular risks. No relationship was found between the change in homocysteine concentration and the presence or absence of the C677T mutation in the MTHFR gene. Homocysteine metabolism was not associated with efficacy or toxicity of MTX treatment.

L2 ANSWER 9 OF 30 MEDLINE on STN

AN 2001689172 MEDLINE
DN PubMed ID: 11698059
TI Doxycycline-induced inhibition of prolidase activity in human skin fibroblasts and its involvement in impaired collagen biosynthesis.
AU Karna E; Palka J; Wolczynski S
CS Department of Medicinal Chemistry, Medical Academy of Bialystok, Kilinskiego 1, PL 15-230, Bialystok, Poland.
SO European journal of pharmacology, (2001 Oct 26) Vol. 430, No. 1, pp. 25-31.
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 11 Dec 2001
Last Updated on STN: 25 Jan 2002
Entered Medline: 3 Jan 2002
AB Several lines of evidence suggest that doxycycline, a semi-synthetic derivative of tetracycline, may be a useful agent in the treatment of osteoarthritis. It inhibits collagen synthesis and collagenase activity in hypertrophic chondrocytes, slowing the process of collagen turnover. However, the mechanism of doxycycline-induced inhibition of these processes has not been established. We considered prolidase, an enzyme involved in collagen metabolism, as a possible target for the doxycycline-induced inhibition of collagen synthesis. Cultured human skin fibroblasts, specialized for collagen synthesis, were used as model cells. Prolidase [E.C. 3.4.13.9] is a manganese-dependent cytosolic exopeptidase that cleaves imidodipeptides containing C-terminal proline, thus providing large amounts of proline for collagen resynthesis. Enzyme activity is regulated through the beta1 integrin receptor. Therefore, we compared the effect of doxycycline on prolidase activity and expression, collagen biosynthesis, gelatinolytic activity and beta1 integrin expression in 24-h treated cultured human skin fibroblasts. We found that doxycycline induced coordinately inhibition of prolidase activity and collagen biosynthesis (IC50 at about 150 microg/ml) and gelatinolytic activity in cultured human skin fibroblasts. The inhibitory effect of doxycycline on the processes was not due to the cytotoxicity of this drug, as shown in the cell viability tetrazoline test. However, an inhibitory effect of the drug on DNA synthesis was observed (IC50 at about 100 microg/ml). The decrease in prolidase activity in fibroblasts treated with doxycycline was not accompanied by any differences in the amount of prolidase or beta1 integrin recovered from these cells, as shown by Western immunoblot analysis. This suggests that the doxycycline-induced down-regulation of prolidase is a post-translational event. The data presented here raise the possibility that the doxycycline-induced decrease in collagen biosynthesis is mostly due to the inhibition of prolidase activity.

L2 ANSWER 10 OF 30 MEDLINE on STN
AN 2000513079 MEDLINE
DN PubMed ID: 11071580
TI Role of collagen hydrolysate in bone and joint disease.
AU Moskowitz R W
CS Case Western Reserve University, Division of Rheumatic Diseases, University Hospitals of Cleveland, OH, USA.
SO Seminars in arthritis and rheumatism, (2000 Oct) Vol. 30, No. 2, pp. 87-99.
Journal code: 1306053. ISSN: 0049-0172.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LA English

FS Priority Journals
EM 200102
ED Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 22 Feb 2001
AB OBJECTIVES: To review the current status of collagen hydrolysate in the treatment of osteoarthritis and osteoporosis. METHODS: Review of past and current literature relative to collagen hydrolysate metabolism, and assessment of clinical investigations of therapeutic trials in osteoarthritis and osteoporosis. RESULTS: Hydrolyzed gelatin products have long been used in pharmaceuticals and foods; these products are generally recognized as safe food products by regulatory agencies. Pharmaceutical-grade collagen hydrolysate (PCH) is obtained by hydrolysis of pharmaceutical gelatin. Clinical studies suggest that the ingestion of 10 g PCH daily reduces pain in patients with osteoarthritis of the knee or hip; blood concentration of hydroxyproline is increased. Clinical use is associated with minimal adverse effects, mainly gastrointestinal, characterized by fullness or unpleasant taste. In a multicenter, randomized, doubleblind, placebo-controlled trial performed in clinics in the United States, United Kingdom, and Germany, results showed no statistically significant differences for the total study group (all sites) for differences of mean pain score for pain. There was, however, a significant treatment advantage of PCH over placebo in German sites. In addition, increased efficacy for PCH as compared to placebo was observed in the overall study population amongst patients with more severe symptomatology at study onset. Preferential accumulation of 14C-labeled gelatin hydrolysate in cartilage as compared with administration of 14C-labeled proline has been reported. This preferential uptake by cartilage suggests that PCH may have a salutary effect on cartilage metabolism. Given the important role for collagen in bone structure, the effect of PCH on bone metabolism in osteoporotic persons has been evaluated. Studies of the effects of calcitonin with and without a collagen hydrolysate-rich diet suggested that calcitonin plus PCH had a greater effect in inhibiting bone collagen breakdown than calcitonin alone, as characterized by a fall in levels of urinary pyridinoline cross-links. PCH appeared to have an additive effect relative to use of calcitonin alone. CONCLUSIONS: Collagen hydrolysate is of interest as a therapeutic agent of potential utility in the treatment of osteoarthritis and osteoporosis. Its high level of safety makes it attractive as an agent for long-term use in these chronic disorders.

L2 ANSWER 11 OF 30 MEDLINE on STN
AN 2000387155 MEDLINE
DN PubMed ID: 10867027
TI Evidence linking chondrocyte lipid peroxidation to cartilage matrix protein degradation. Possible role in cartilage aging and the pathogenesis of osteoarthritis.
AU Tiku M L; Shah R; Allison G T
CS Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey 08903-0019, USA.. tikuml@umdnj.edu
SO The Journal of biological chemistry, (2000 Jun 30) Vol. 275, No. 26, pp. 20069-76.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 18 Aug 2000
Last Updated on STN: 18 Aug 2000
Entered Medline: 10 Aug 2000
AB Reactive oxygen species (ROS) are implicated in both cartilage aging and the pathogenesis of osteoarthritis. We developed an in vitro

model to study the role of chondrocyte-derived ROS in cartilage matrix protein degradation. Matrix proteins in cultured primary articular chondrocytes were labeled with [(3)H]proline, and the washed cell matrix was returned to a serum-free balanced salt solution. Exposure to hydrogen peroxide resulted in oxidative damage to the cell matrix as established by monitoring the release of labeled material into the medium. Calcium ionophore treatment of chondrocytes, in a dose-dependent manner, significantly enhanced the release of labeled matrix, suggesting a chondrocyte-dependent mechanism of matrix degradation. Antioxidant enzymes such as catalase or superoxide dismutase did not influence matrix release by the calcium ionophore-activated chondrocytes. However, vitamin E, at physiological concentrations, significantly diminished the release of labeled matrix by activated chondrocytes. The fact that vitamin E is a chain-breaking antioxidant indicates that the mechanism of matrix degradation and release is mediated by the lipid peroxidation process. Lipid peroxidation was measured in chondrocytes loaded with cis-parinaric acid. Both resting and activated cells showed constitutive and enhanced levels of lipid peroxidation activity, which were significantly reduced in the presence of vitamin E. In an immunoblot analysis, malondialdehyde and hydroxynonenal adducts were observed in chondrocyte-matrix extracts, and the amount of adducts increased with calcium ionophore treatment . Furthermore, vitamin E diminished aldehyde-protein adduct formation in activated extracts, which suggests that vitamin E has an antioxidant role in preventing protein oxidation. This study provides in vitro evidence linking chondrocyte lipid peroxidation to cartilage matrix protein (collagen) oxidation and degradation and suggests that vitamin E has a preventive role. These observations indicate that chondrocyte lipid peroxidation may have a role in the pathogenesis of cartilage aging and osteoarthritis.

L2 ANSWER 12 OF 30 MEDLINE on STN
AN 2000312659 MEDLINE
DN PubMed ID: 10855951
TI Effects of methotrexate on nucleotide pools in normal human T cells and the CEM T cell line.
AU Budzik G P; Colletti L M; Faltynek C R
CS Abbott Laboratories, Pharmaceutical Products Division, Abbott Park, Illinois 60064, USA.. jerry.p.budzik@abbott.com
SO Life sciences, (2000) Vol. 66, No. 23, pp. 2297-307.
Journal code: 0375521. ISSN: 0024-3205.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200006
ED Entered STN: 6 Jul 2000
Last Updated on STN: 6 Jul 2000
Entered Medline: 29 Jun 2000
AB It has been proposed that the clinical utility of methotrexate (MTX) in the treatment of rheumatoid arthritis may be due, in part, to inhibition of 5-amino imidazole-4-carboxamide ribonucleotide formyltransferase (AICARFT) by polyglutamated forms of MTX. AICARFT is the second folate dependent enzyme in de novo purine biosynthesis. In this study, the effects of MTX on de novo purine biosynthesis as well as total nucleotide pools were evaluated in both the human T cell line, CEM, and phytohemagglutinin-activated normal human T lymphocytes. De novo synthesized purines were metabolically labeled with 14C-glycine after MTX treatment and analyzed by HPLC. In normal T cells, MTX produced a dose-dependent reduction in de novo adenosine and guanosine pools with maximal effects (>50%) at 1 microM MTX. In CEM cells, de novo purine synthesis was almost completely blocked by 1 microM MTX. Total purine pools were also reduced in both cell types after MTX treatment. Since 1 microM MTX caused almost complete growth inhibition in CEM cells, we evaluated whether growth could be reconstituted with exogenous purine bases and pyrimidine nucleosides which

can be utilized via salvage pathways. The combination of hypoxanthine and thymidine substantially reversed growth inhibition with 1 microM MTX in CEM cells. Taken together, these results demonstrate that MTX inhibits de novo nucleotide synthesis in T cells and suggest that AICARFT inhibition may be one aspect of the multi-site mechanism of MTX action in the treatment of rheumatoid arthritis.

L2 ANSWER 13 OF 30 MEDLINE on STN
AN 2000044298 MEDLINE
DN PubMed ID: 10579697
TI Screening neutral and acidic IgG N-glycans by high density electrophoresis.
AU Frears E R; Merry A H; Axford J S
CS Academic Unit of Musculoskeletal Disease, St. George's Hospital Medical School, London.. e.frears@sghms.ac.uk
SO Glycoconjugate journal, (1999 Jun) Vol. 16, No. 6, pp. 283-90.
Journal code: 8603310. ISSN: 0282-0080.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 13 Jan 2000
Last Updated on STN: 13 Jan 2000
Entered Medline: 15 Dec 1999
AB IgG carries bi-antennary N-linked glycans which differ in degrees of galactosylation, core fucosylation and bisecting N-acetyl glucosamine. The majority of these are non-sialyated closely related neutral structures which can be resolved by HPLC analysis, but which are difficult to separate in techniques such as fluorophore-coupled carbohydrate electrophoresis. Derivatisation with the singly charged fluorophore, 2-amino benzoic acid and separation in gels with a 30% monomer content in tris/glycine buffer enabled separation of neutral glycans. In particular, agalactosyl glycans with either a core fucose substitution or bisecting N-acetyl galactosamine could be resolved. Good separation of mono- and di-galactosylated glycans was also achieved with this system. It was shown that IgG can be separated from serum by size-exclusion and anion exchange chromatography with minimal contamination, with complete glycan release accomplished by the enzyme peptide-N-glycosidase F (F. meningosepticum). This method of resolving IgG glycans could be used to monitor patients in which glycosylation changes may have a diagnostic value, as in rheumatoid arthritis. It could also be used to monitor recombinant IgG glycosylation where routine screening is required in the biotechnology industry.

L2 ANSWER 14 OF 30 MEDLINE on STN
AN 1999386776 MEDLINE
DN PubMed ID: 10452833
TI Proliferation and collagen synthesis of human anterior cruciate ligament cells in vitro: effects of ascorbate-2-phosphate, dexamethasone and oxygen tension.
AU Fermor B; Urban J; Murray D; Pocock A; Lim E; Francis M; Gage J
CS Nuffield Department of Orthopaedic Surgery, Nuffield Orthopaedic Centre, Headington, Oxford, OX3 7LD, U.K.
SO Cell biology international, (1998) Vol. 22, No. 9-10, pp. 635-40.
Journal code: 9307129. ISSN: 1065-6995.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 5 Oct 1999
Last Updated on STN: 5 Oct 1999
Entered Medline: 23 Sep 1999
AB Clinical and experimental studies demonstrate that injured anterior

cruciate ligaments (ACL) do not usually heal and that autografts used to repair the ACL rapidly weaken in the early period and take a long time to regain strength. The aim of this study was to develop an in vitro culture system in which environmental and biochemical factors influencing the proliferation and matrix synthesis of cells derived from human anterior cruciate ligaments can be studied. Primary cultures of human ACL cells were obtained by outgrowth from explants of normal ACL obtained at knee replacement for osteoarthritis in Dulbecco's minimum essential medium (DMEM). The effects of the additives 100 microm L-ascorbic acid-2-phosphate (Asc-2-P) and 10 n m dexamethasone (dex) on proliferation and collagen synthesis were assessed after 4, 8 and 12 days in culture. Ligament cells were grown at 0, 5, 10 and 21%p O(2)in the presence of 100 microm asc-2-P and 10 n m dex. DNA content was assessed using the Hoechst dye method and collagen synthesis by the incorporation of 5 mCi/ml [(3)H]proline after 3, 6 and 12 days in culture.At 21%p O(2), the presence of asc-2-P and dex induced significantly greater (P< 0.01, ANOVA) cell proliferation than with either additives alone. Greatest percentage collagen to total protein synthesis was observed when cells were grown in the presence of asc-2-P only. Least proliferation and percentage collagen to total protein synthesis was seen when both additives were omitted. Greatest cell proliferation was seen when cells were grown in 10%p O(2)and 5%p O(2)was associated with increased collagen synthesis.These results suggest that it is possible to study the effects of environmental and biochemical factors on human ACL healing in vitro. Our data suggest oxygen can influence certain biosynthetic activities of ACL cells. Low oxygen tensions lead to an increase in collagen production by ACL cells. However early responses to injury require extensive cell proliferation which may be activated at higher p O(2). Variation of p O(2)in ligaments during healing may therefore be an important modulator of successful repair.

L2 ANSWER 15 OF 30 MEDLINE on STN
AN 1998357093 MEDLINE
DN PubMed ID: 9692064
TI Acute synovitis and intra-articular methylprednisolone acetate in ponies.
AU Todhunter R J; Fubini S L; Vernier-Singer M; Wootton J A; Lust G; Freeman K P; MacLeod J N
CS Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA.
SO Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, (1998 Mar) Vol. 6, No. 2, pp. 94-105.
Journal code: 9305697. ISSN: 1063-4584.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 17 Sep 1998
Last Updated on STN: 17 Sep 1998
Entered Medline: 10 Sep 1998
AB OBJECTIVE: To determine how acute synovitis, with and without intra-articular methylprednisolone acetate (MPA), affect synthesis of proteoglycan, total protein, and collagen in articular cartilage and total protein synthesis in synovial membrane. DESIGN: Synovitis was induced in 10 ponies by the injection of 0.5 ng lipopolysaccharide (LPS) into the left radiocarpal and midcarpal joints every 2 days for a total of four treatments. Synovitis was documented by clinical examination and synovial fluid analyses. Two days before euthanasia, MPA (0.1 mg/kg) was injected with the last dose of LPS into both the left and right radiocarpal and midcarpal joints of five of these ponies. Proteoglycan synthesis in articular cartilage explants from these joints was measured by incorporation of sodium [35S]sulfate. The size of the proteoglycan monomers and their aggregation with hyaluronan was assessed by size-exclusion chromatography. Protein synthesis in articular

cartilage was measured by incorporation of [3H]proline and collagen synthesis by conversion of [3H]proline into [3H]hydroxyproline. Protein synthesis was measured in synovial membrane explants by incorporation of [35S]methionine. RESULTS: Ponies developed carpal effusion and mild lameness accompanied by increased total nucleated cell count and total solids in synovial fluid in response to the LPS injections. Moderate to severe synovial membrane proliferation and inflammation were observed histopathologically in joints injected with LPS but no consistent light-microscopical changes were observed in the articular cartilage from these joints. Intra-articular MPA alone was associated with decreased proteoglycan synthesis and increased protein and collagen synthesis in the cartilage explants. Total protein synthesis by synovial membrane was also increased by MPA alone. In contrast, no differences in protein or proteoglycan synthesis were observed in explants from the joints with synovitis, with or without intra-articular MPA. Treatment with MPA, LPS, and LPS/MPA did not alter proteoglycan aggregate size, but LPS-induced synovitis resulted in an increase in the second largest population of monomers. MPA increased the synthesis of small proteoglycan monomers. CONCLUSION: Based on the methods used, acute synovitis prevented changes induced by intra-articular MPA alone. Results suggested that the effect of intra-articular MPA on joint metabolism was different between inflamed and normal joints. Experimental studies must consider the effect of inflammation, as well as the potential to introduce in vitro culture artifacts when investigating the effect of intra-articular corticosteroids on chondrocyte function.

L2 ANSWER 16 OF 30 MEDLINE on STN
AN 1998261679 MEDLINE
DN PubMed ID: 9599313
TI Salivary acidic proline-rich proteins in rheumatoid arthritis.
AU Jensen J L
CS Department of Oral Surgery and Oral Medicine, University of Oslo, Norway.. jljensen@odont.uio.no
SO Annals of the New York Academy of Sciences, (1998 Apr 15) Vol. 842, pp. 209-11.
Journal code: 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 25 Jun 1998
Last Updated on STN: 25 Jun 1998
Entered Medline: 18 Jun 1998
AB In an ongoing attempt to investigate qualitative salivary parameters in diseases affecting salivary glands, patients with rheumatoid arthritis (RA) were examined. Patients were selected from the Oslo RA register for the present study if they fulfilled the following criteria: age 52-74 years, disease duration 10-20 years, and disability score as assessed by the Modified Health Assessment Questionnaire < or = 2.5. From these 105 patients, two subgroups of patients were selected, one group with pronounced sicca symptoms from eyes and mouth, and one group without such symptoms. Sicca symptoms were assessed using a postal questionnaire with the questions on dry mouth and dry eyes of the European classification criteria for Sjogren's syndrome. Patients were excluded from further examinations if they used medication that could cause dryness in eyes or mouth. Thus, nine patients remained in the sicca group (having four or more sicca symptoms), and ten matched RA patients were selected for the nonsicca group. A healthy sex- and age-matched control group (n = 10) was also examined. In a preliminary report we have shown that differences in flow rates between sicca and nonsicca RA patients were limited to lower values of unstimulated whole saliva. To further evaluate salivary changes in RA, a disease frequently associated with secondary

Sjogren's syndrome, we have studied qualitative salivary parameters in these patients,' including secretory rates of proline-rich proteins (PRPs), statherins, and histatins. In the present report, phenotypes of PRPs, the ratio of PRPs derived from the two loci (PRH1 and PRH2), and PRP concentration and output in parotid and submandibular saliva derived from the two loci are presented. Parotid (PS) and submandibular saliva (SS) were collected from all individuals using 2% citric acid as a saliva stimulus. PRPs in PS and SS were identified using a SMART microchromatographic system with a Mono Q column and a Tris-HCl/NaCl gradient (method adapted from reference 5). For PRPs, the primary polypeptide products are coded for on two loci (PRH1 and PRH2), which have three and two commonly occurring gene variants, respectively. On PRH1, the proteins PIF-s, Db-s, and Pa are coded for, whereas PRP-1 and PRP-2 are coded for on the PRH2 locus. As each protein variant has a postranscriptional cleavage product, individuals will exhibit four, six, or eight PRPs in their saliva, depending on whether they are homozygous at both, one, or neither of the two loci. Accordingly, 18 possible phenotypes may exist, but as few as three phenotypes were found in 79% of the 127 healthy individuals examined by Hay et al. The SMART system allows the determination of the different acidic PRPs present in saliva. Concentrations of the various phenotypes were calculated by peak integration versus pure PRP standards. Total PRP concentration derived from each locus was calculated as the sum of the concentrations of PRP variants from that locus.

L2 ANSWER 17 OF 30 MEDLINE on STN
AN 94259003 MEDLINE
DN PubMed ID: 8200300
TI Insulin autoimmune syndrome (Hirata disease): clinical features and epidemiology in Japan.
AU Uchigata Y; Eguchi Y; Takayama-Hasumi S; Omori Y
CS Diabetes Center, Tokyo Women's Medical College, Japan.
SO Diabetes research and clinical practice, (1994 Jan) Vol. 22, No. 2-3, pp. 89-94.
Journal code: 8508335. ISSN: 0168-8227.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199407
ED Entered STN: 14 Jul 1994
Last Updated on STN: 14 Jul 1994
Entered Medline: 1 Jul 1994
AB Since Hirata et al. first reported a patient with insulin autoimmune syndrome in 1970, 197 cases have been reported in Japan as of December, 1992. The clinical profiles of these 197 cases were as follows; the peak age at onset was 60-69 years and peak duration of hypoglycemic attacks was more than 1 and less than 3 months. There was no gender difference in the peak age of onset or duration of hypoglycemic attacks. Approximately 82% of the IAS patients had spontaneous remission without any positive treatment. Before diagnosis of IAS, 43% of the patients with IAS had been taking medication; methimazole (MTZ) for Graves' disease, alpha-mercaptopropionyl glycine (MPG) for cataracts, liver disease or rheumatoid arthritis, or glutathione for liver disease, all of which are sulfhydryl compounds. After such sulfhydryl compounds were discontinued, the hypoglycemic attacks subsided. Three patients with IAS experienced recurrence of the hypoglycemic attacks after re-administration of MTZ and MPG, although 6 patients who developed IAS without exposure to any drug had recurrent attacks without exposure to any drug around 1 year after the first hypoglycemic attacks had stopped. Thus, hypoglycemia in IAS is mainly transient and the development of IAS may be related to sulfhydryl compounds.

L2 ANSWER 18 OF 30 MEDLINE on STN
AN 94208866 MEDLINE

DN PubMed ID: 7512531
TI Isolation and characterization of a cartilage-specific membrane antigen (CH65): comparison with cytokeratins and heat-shock proteins.
AU Bang H; Mollenhauer J; Schulmeister A; Nager C; van Eden W; Wand-Wurttenberger A; Kaufmann S H; Brune K
CS Institute of Pharmacology and Toxicology, Erlangen, Germany.
SO Immunology, (1994 Feb) Vol. 81, No. 2, pp. 322-9.
Journal code: 0374672. ISSN: 0019-2805.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199405
ED Entered STN: 26 May 1994
Last Updated on STN: 29 Jan 1996
Entered Medline: 17 May 1994
AB We report the isolation and characterization of a 65,000 MW chondrocyte autoantigen (CH65) which may be involved in rheumatoid arthritis. This chondrocyte-specific antigen reacted with sera from patients with rheumatoid arthritis (RA). CH65 did not cross-react with a polyclonal antibody raised against microbial heat-shock protein (hsp) 65, anti-human hsp 65 monoclonal antibodies (mAb) (LK1 and LK2), anti-microbial hsp 65 mAb (IA10, IIC8 and WTB-78H1) and anti-cytokeratin 8, 18, 19 mAb (NCL5D3MAb). CH65 could be purified from chicken chondrocyte membranes by ammonium sulphate precipitation and a novel electro-gel-filtration method. The amino acid analysis yielded an unusually high degree of glycine, serine and asparagine residues. The internal amino acid sequence obtained by tryptic digestion revealed homologies with the cytokeratin family. Despite these homologies, CH65 lacked immunological cross-reactivity with commercial anti-cytokeratin antibodies. Mice mAb generated against the purified CH65 (C6) were used to identify the protein as a tissue-specific constitutive protein membrane from chondrocytes. Sera from patients with RA cross-reacted with purified CH65. The stress or heat-shock protein (hsp 65), implicated in the development of experimental and clinical arthritis, showed no immunological cross-reactivity with CH65 in Western blots. These findings suggest that CH65 may represent an interesting cartilage-specific new antigen in RA. The availability of this antigen in purified form and specific mAb may offer useful tools in arthritis research.

L2 ANSWER 19 OF 30 MEDLINE on STN
AN 94163177 MEDLINE
DN PubMed ID: 8118455
TI [Effect of diacerhein (ART 50) on the matrix synthesis and collagenase secretion by cultured joint chondrocytes in rabbits].
Effet de la diacerheine (ART 50) sur la synthese de la matrice et la secretion de collagenase par des chondrocytes articulaires de lapin en culture.
AU Boittin M; Redini F; Loyau G; Pujol J P
CS Laboratoire de Biochimie du Tissu Conjonctif, CHU Cote de Nacre, Caen, Paris.
SO Revue du rhumatisme (Ed. francaise : 1993), (1993 Jul) Vol. 60, No. 6 Pt 2, pp. 68S-76S.
Journal code: 9315664. ISSN: 1169-8330.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 199404
ED Entered STN: 12 Apr 1994
Last Updated on STN: 12 Apr 1994
Entered Medline: 4 Apr 1994
AB Cultured rabbit joint chondrocytes were exposed to diacerhein (DAR : ART 50, Negma, 10(-6) to 10(-4) M), which has proved effective and safe when

given for two months for the treatment of osteoarthritis . Experiments were performed with and without 500 pg/ml human recombinant interleukin-1 to determine whether diacerhein antagonizes the effects of this monokine. Glycosaminoglycan production was measured by 35S-sulfate incorporation followed by cetylpyridinium precipitation, collagen production by 3H-proline labeling and bacterial collagenase digestion, and collagenase production by determination of the amount of 3H-collagen that underwent degradation. Incubation of chondrocytes with diacerhein for 24 hours was not associated with substantial changes in glycosaminoglycan or collagen production but substantially antagonized interleukin-1-mediated enhancement of collagenase production. With longer incubation periods (6 days) with the 10(-6) M concentration of diacerhein, production of glycosaminoglycans and collagen increased. Incubation with both diacerhein and interleukin-1 for six days partly antagonized the cytokine's inhibitory effect on glycosaminoglycan and collagen production. During these experiments, the medium's ability to break down collagen was consistently reduced by diacerhein, even in the presence of interleukin-1. These data demonstrate that diacerhein can reduce or even abolish interleukin-1-mediated enhancement of collagenase production by joint chondrocytes. This effect may lead to less erosion of cartilage in degenerative joint diseases.

L2 ANSWER 20 OF 30 MEDLINE on STN
AN 93293116 MEDLINE
DN PubMed ID: 8514235
TI Immunogenetic analysis of rheumatoid arthritis in the Japanese population.
AU Tsuchiya K
CS Department of Genetics, Kyushu University, Fukuoka.
SO Fukuoka igaku zasshi = Hukuoka acta medica, (1993 Feb) Vol. 84, No. 2, pp. 68-78.
Journal code: 9423321. ISSN: 0016-254X.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 199307
ED Entered STN: 6 Aug 1993
Last Updated on STN: 6 Aug 1993
Entered Medline: 20 Jul 1993
AB To reveal immunogenetic factors involved in the pathogenesis of rheumatoid arthritis(RA), two hundreds and four unrelated Japanese patients with RA were typed for HLA by both serologic typing and DNA typing using polymerase chain reaction-sequence specific oligonucleotide probe (PCR-SSOP) method. Serologic HLA typing data showed that frequencies of HLA-A11, DR4, DR53, and DQ4 were increased and those of DR8, DR52, and DQ1 were decreased in the patient group. The HLA-DNA typing has defined more precisely the disease-associated HLA-class II alleles and revealed that DRB1*0405, DQA1*03, and DQB1*0401 were strongly associated with the disease susceptibility whereas DRB1*0803, DQA1*0103, and DQB1*0601 showed negative association with RA. Comparison of amino acid sequences of DRB1*0405 with other DRB1 alleles suggested that the risk for RA was closely associated with particular amino acid residues of DR beta chain, i. e. glycine residue at the 86th position in addition to the residues between 70th and 74th position. The significant decreased frequency of DRB1*0803 in the DRB1*0405 positive patient group suggests that DRB1*0803 may control resistance to RA as a dominant genetic trait. In addition, the observation that the frequency of DPB1*0201 was increased in the DRB1*0405 negative patient group may indicate that the disease susceptibility to RA is controlled by the HLA-DP region in the minority of the patients. The polymorphism of TAP2 gene and TCR genes showed no significant association with RA, suggesting that the contribution of these genes to the susceptibility is relatively small, if any.

L2 ANSWER 21 OF 30 MEDLINE on STN

AN 92324289 MEDLINE
DN PubMed ID: 1339352
TI Molecular analysis of the V kappa III-J kappa junctional diversity of polyclonal rheumatoid factors during rheumatoid arthritis frequently reveals N addition.
AU Martin T; Blaison G; Levallois H; Pasquali J L
CS Laboratoire d'immunopathologie, Hopital Civil, Strasbourg, France.
SO European journal of immunology, (1992 Jul) Vol. 22, No. 7, pp. 1773-9.
Journal code: 1273201. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-S39395; GENBANK-V00556; GENBANK-X54839; GENBANK-X63401; GENBANK-Z14238; GENBANK-Z14239; GENBANK-Z14240; GENBANK-Z14241; GENBANK-Z14242; GENBANK-Z14243
EM 199208
ED Entered STN: 21 Aug 1992
Last Updated on STN: 21 Aug 1992
Entered Medline: 11 Aug 1992
AB Much interest was stirred in recent years by the evidence that rheumatoid factors (RF) variable regions are encoded by a restricted set of V genes, with little or no somatic mutations, that are often overexpressed in the fetal repertoire. This is reminiscent of what has been observed for natural autoantibodies. However, these data come from studies of monoclonal RF (mRF) isolated from patients with lymphoproliferative disorders who usually do not present autoimmune symptoms. The molecular characterization of RF during autoimmune diseases such as rheumatoid arthritis (RA) has been hampered for some time because of their polyclonality; recently using the polymerase chain reaction method, we have demonstrated that RF kappa variable regions from a patient with RA were encoded by V kappa III genes known to code for mRF but that these genes had undergone somatic mutations with a pattern suggesting an antigen-driven maturation. Because an important role of the light chain third complementarity-determining region (CDR3) in anti-IgG reactivity and idiotype expression has already been suspected for RF, we now report the molecular characterization of the junction regions of these rearranged V kappa gens. Surprisingly, our data show that in 55% of the cases there is addition of a proline and/or glycine amino acid residue at the recombination site between V kappa and J kappa. The sequence analysis of our patients' germ-line Vg and J kappa 4 genes segments and their flanking regions demonstrates that the additional codons are not readily explicable by recombination between germ-line sequences and probably result from an N addition process. Since we could not find such an additional codon in 15 previously published mRF kappa chains we suggest that "pathogenic" RF during RA and mRF derive from different, although overlapping, B cell subsets. Moreover, since additional codons at the recombination site of V kappa and J kappa seem exceptional in expressed human kappa chains and because the resulting amino acid residue is a proline in most cases, we think that RF kappa chain CDR3 is under a very strong selective pressure during RA.

L2 ANSWER 22 OF 30 MEDLINE on STN
AN 92164141 MEDLINE
DN PubMed ID: 1790625
TI Clinical analysis in intact erythrocytes using 1H spin echo NMR.
AU Reglinski J; Smith W E; Wilson R; Buchanan L M; McKillop J H; Thomson J A; Brzeski M; Marabani M; Sturrock R D
CS Department of Pure and Applied Chemistry, Strathclyde University, Glasgow, UK.
SO Clinica chimica acta; international journal of clinical chemistry, (1991 Sep 14) Vol. 201, No. 1-2, pp. 45-57.
Journal code: 1302422. ISSN: 0009-8981.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 199204
ED Entered STN: 17 Apr 1992
Last Updated on STN: 17 Apr 1992
Entered Medline: 2 Apr 1992
AB A new method of clinical analysis based on 1H spin echo NMR spectroscopy is presented. It is capable of providing information on six metabolites within viable erythrocytes, directly and without any preparative procedures prior to analysis except for cell separation and washing. Erythrocytes from patients with rheumatoid arthritis and Graves' disease are compared with cells obtained from healthy volunteers. The NMR detectable species in the cytosol of the cells are glutathione, ergothioneine, choline, creatine, glycine , lactate and to a lesser extent alanine and valine. Significant differences are observed between the ergothioneine pools in the rheumatoid group (P less than 0.01) compared to the control group. The glutathione: di-glutathione ratio can be assessed from the ratio, g2 to g4, taken from different signals in the glutathione molecule. The total concentration of glutathione present is easily assessed qualitatively but is more difficult to quantitate.

L2 ANSWER 23 OF 30 MEDLINE on STN
AN 90075532 MEDLINE
DN PubMed ID: 2686878
TI Ochronosis: a report of a case and a review of literature.
AU Konttinen Y T; Hoikka V; Landtman M; Saari H; Santavirta S; Metsarinne K; Seegmiller J E
CS Fourth Department of Medicine, Helsinki University Central Hospital, Finland.
SO Clinical and experimental rheumatology, (1989 Jul-Aug) Vol. 7, No. 4, pp. 435-44. Ref: 9
Journal code: 8308521. ISSN: 0392-856X.
CY Italy
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199001
ED Entered STN: 28 Mar 1990
Last Updated on STN: 28 Mar 1990
Entered Medline: 25 Jan 1990
AB A patient with alkaptonuria and ochronotic pigment deposited in articular cartilage and sclerae clinically manifested a serious osteoarthritis of the peripheral and axial joints and synchondrosis, typically involved in long lasting cases of this hereditary defect of homogentisic acid oxidase. This is the first patient with this disorder reported, where a non-cemented total knee prosthesis (PCAR) was applied on both knees. This was possible due to the good quality of the bone stock, which did not seem to be impaired by ochronosis. Our patient had no cardiac symptoms or murmurs, but had a slight calcification in the annulus of aorta observed with echocardiography, a useful new method for screening this disease manifestation. A third new aspect reported is the immunopathology of the synovial tissue. Small pieces of torn-off cartilage were seen embedded in the synovial stroma. This was associated with a slight hyperplasia of the C3bi-receptor positive and proline hydroxylase positive type A and B synovial lining cells. Perivenular infiltrates contained CD2 positive T lymphocytes, mostly belonging to the CD4 subset, and some C3bi-receptor positive monocytes. Activated CD25 positive and immunoglobulin light chain positive T and B lymphocytes were absent or few. Because modern medicine has much to offer to those suffering from this ancient inborn error of metabolism in the form of new specific diagnostic methods and new surgical modes of treatment, such as endoprosthesis surgery and

cardiac valve replacement, we also present a literature overview of this interesting condition.

L2 ANSWER 24 OF 30 MEDLINE on STN
AN 87240438 MEDLINE
DN PubMed ID: 3036026
TI Retinoid modulation of collagenase production by adherent human mononuclear cells in culture.
AU Ohta A; Louie J S; Uitto J
NC AM-28450 (NIADDK)
AM-35297 (NIADDK)
GM-28833 (NIGMS)
SO Annals of the rheumatic diseases, (1987 May) Vol. 46, No. 5, pp. 357-62.
Journal code: 0372355. ISSN: 0003-4967.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198707
ED Entered STN: 5 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 23 Jul 1987
AB Previous observations have suggested that retinoids might be useful for the treatment of rheumatoid arthritis. In this study we examined the effects of various retinoids on collagenase production by adherent human peripheral blood mononuclear cells in culture. We have previously shown that these cells, consisting predominantly of monocyte-macrophages, actively synthesize and secrete collagenase upon stimulation with concanavalin A. The cells were incubated in serum free medium with all-trans-retinoic acid, 13-cis-retinoic acid, all-trans-retinal, or Ro 10-9359 (trimethylmethoxyphenyl retinoic acid ethyl ester) for up to 72 hours, and the collagenase activity was determined with [3H]proline labelled type I collagen as substrate. The incubation of mononuclear cells with all-trans-retinoic acid in the concentration range 10(-7)-10(-5) mol/l resulted in a dose dependent inhibition of the collagenase production. All-trans-retinal was also a potent inhibitor, whereas 13-cis-retinoic acid and Ro 10-9359 in a concentration of 10(-5) mol/l had a lesser effect. Control experiments indicated that the inhibition of collagenase production by all-trans-retinoic acid did not result from inhibition of total protein synthesis nor could it be explained by induction of an inhibitory molecule. These results indicate that retinoids with distinct structural features can inhibit collagenase production by monocyte-macrophages, and suggest a role for retinoids in the treatment of rheumatoid arthritis.

L2 ANSWER 25 OF 30 MEDLINE on STN
AN 86303340 MEDLINE
DN PubMed ID: 3017876
TI In vitro production of collagen by synovial fibroblasts from D-penicillamine-treated arthritic rabbits.
AU Brisset M; Pujol J P; Penfornis H; Farjanel J; Rattner A; Bocquet J; Beliard R; Loyau G
SO International journal of tissue reactions, (1986) Vol. 8, No. 4, pp. 271-8.
Journal code: 8302116. ISSN: 0250-0868.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198610
ED Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 3 Oct 1986
AB In order to get further insight into the mechanism of D-penicillamine

action on synovial tissue collagen synthesis, fibroblasts derived from drug-treated arthritic rabbits were cultured and labelled with radioactive proline. No evident correlation was found between the amount of newly synthesized collagen and the previous treatment of animals. In contrast, the prolyl-hydroxylase activity was reduced in cells from rabbits receiving D-penicillamine. This finding suggests that culture conditions may influence the collagen-synthesizing potentiality of the synovial fibroblasts without changing the level of enzyme activity. Therefore, the prolyl-hydroxylase activity could be considered here as a more reliable reflection of the in vivo situation. The ratio of type III to type I procollagens, as estimated by DEAE-cellulose chromatography, showed a rise in cultures from D-penicillamine-treated rabbits as compared to controls. This result indicates that long-term administration of the drug may alter the collagen composition of synovial tissue matrix in rheumatoid arthritis. The question remains, however, whether this alteration contributes to the beneficial effect of the drug.

L2 ANSWER 26 OF 30 MEDLINE on STN
AN 86096552 MEDLINE
DN PubMed ID: 4081662
TI Plasma amino acids in rheumatoid arthritis.
AU Trang L E; Furst P; Odeback A C; Lovgren O
SO Scandinavian journal of rheumatology, (1985) Vol. 14, No. 4, pp. 393-402. Journal code: 0321213. ISSN: 0300-9742.
CY Sweden
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198602
ED Entered STN: 21 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 10 Feb 1986
AB Plasma amino acid concentrations have been investigated in 12 female patients with rheumatoid arthritis (RA), who were hospitalized for two 14-day periods, one of which included 7 days of total fasting, whereas the other served as control period with normal food intake. All medical treatment was stopped on admission to the hospital. Plasma amino acid levels were repeatedly determined during both periods. Another group, consisting of 8 healthy volunteers, also underwent total fasting, for 6 days. The response to food deprivation with regard to plasma amino acid levels was compared with that in the RA patients. The results obtained from the control period were compared with those derived from age and sex matched healthy controls. RA disease was not characterized by a typical amino acid pattern. Major increases were seen in the concentrations of taurine, aspartate, glutamate, glycine, 1-methyl histidine, isoleucine and arginine. Rather smaller yet significant elevations could be observed in the levels of cystein, threonine, serine, citrulline, methionine and leucine. The only amino acid to show a lowered concentration was alpha-aminobutyrate. Most of the alterations induced by fasting were similar to those in healthy volunteers. An exception was the levels of taurine, which evidenced in RA patients a further increase during starvation, not observed in healthy volunteers, and valine which exhibited, a smaller increment than that apparent in healthy controls. The increase in sulphur-containing amino acids might be interpreted as a sign of an enhanced glutathione (GSH) catabolism, whereas the differing metabolic behaviour of branched chain amino acids (BCAA) suggests a specific reaction of valine in RA disease, similar to that in other catabolic diseases.

L2 ANSWER 27 OF 30 MEDLINE on STN
AN 80213600 MEDLINE
DN PubMed ID: 7384724
TI [Tiopronine, new anti-rheumatic drug, has slow action in rheumatoid arthritis].
La tiopronine, nouvel anti-rhumatismal a action lente dans la polyarthrite

rhumatoide.
AU Amor B; Mery C; de Gery A
SO Revue du rhumatisme et des maladies osteo-articulaires, (1980 Mar) Vol. 47, No. 3, pp. 157-62.
Journal code: 0407211. ISSN: 0035-2659.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA French
FS Priority Journals
EM 198008
ED Entered STN: 15 Mar 1990
Last Updated on STN: 15 Mar 1990
Entered Medline: 25 Aug 1980
AB 2 mercapto propionyl glycine (tiopronine) has, like D-penicillamine, a thiol radicle; it is a powerful chelating agent of heavy metals. This analogy suggests that it may be used in rheumatoid arthritis. A preliminary double blind study lasting four months comparing 1g./day in 20 patients and a placebo in 10 patients showed slight (non significant) efficacy concerning all parameters. An open study using 1.5 g. daily is being carried out in 32 patients, and we note a beneficial effect on the morning stiffness, the joint index, the functional index, the prehension strength, the E.S.R., and the joint swelling. The side effects are similar to those of D-penicillamine: loss of taste, proteinuria, mucous ulceration, which required stopping treatment. The therapeutic effect within 4 months and was maintained for 18 months in the 15 patients under treatment. A new double blind trial comparing placebo and tiopronine at a dose of 1.5 g. daily is in progress.

L2 ANSWER 28 OF 30 MEDLINE on STN
AN 79203073 MEDLINE
DN PubMed ID: 451491
TI Skin collagen biosynthesis in patients with rheumatoid arthritis treated with D-penicillamine.
AU Schorn D; Francis M J; Loudon M; Mowat A G
SO Scandinavian journal of rheumatology, (1979) Vol. 8, No. 2, pp. 124-8.
Journal code: 0321213. ISSN: 0300-9742.
CY Sweden
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197909
ED Entered STN: 15 Mar 1990
Last Updated on STN: 15 Mar 1990
Entered Medline: 1 Sep 1979
AB Collagen biosynthesis was measured in skin biopsies taken from 13 patients with rheumatoid arthritis before and after at least 6 months' continuous treatment with D-penicillamine, 1.0 g/day. There was a significant 36% reduction in mean collagen biosynthesis (p less than 0.0125) as assayed by 14C-hydroxyproline formation from 14C-proline during 24 h of tissue culture. The changes in 14C-hydroxyproline formation were correlated with the total doses of D-penicillamine taken (r = 0.71, p less than 0.01) and the falls in ESR (r = 0.72, p less than 0.01). No significant change in general protein syntehsis was observed. 500 microgram/mlD-penicillamine added to skil cultures in vitro inhibited both collagen and general protein synthesis (p less than 0.01). It is suggested that the clinical improvement induced by D-penicillamine could reflect an inhibition of collagen proliferation in the synovium.

L2 ANSWER 29 OF 30 MEDLINE on STN
AN 78219328 MEDLINE
DN PubMed ID: 97351
TI A simple routine method for detecting hidden rheumatoid factors.
AU Hansson U B; Winblad S

SO Journal of immunological methods, (1978) Vol. 22, No. 1-2, pp. 155-64.
Journal code: 1305440. ISSN: 0022-1759.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197809
ED Entered STN: 14 Mar 1990
Last Updated on STN: 14 Mar 1990
Entered Medline: 15 Sep 1978
AB A new and simple routine method is described for detecting hidden rheumatoid factors in human serum. EDTA glycine and NaCl were used to liberate hidden rheumatoid factors and to inactivate complement before rheumatoid-factor activity was determined in a glycine--NaCl solution. Forty-nine out of 97 sera from individuals with seronegative rheumatoid arthritis gave positive reactions by this method. Rheumatoid sera with low titres by standard tests gave higher titres with the new method. The new method detects both IgM and IgG rheumatoid factors and is simple and suitable for use in routine medical laboratories. Used in parallel with the classical tests, it facilitates detection of hidden rheumatoid factors.

L2 ANSWER 30 OF 30 MEDLINE on STN
AN 77143867 MEDLINE
DN PubMed ID: 1022870
TI Penicillamine in rheumatoid arthritis. Connective tissue changes and alterations in serum copper and phase reactants in relation to clinical improvement.
AU Hansen T M; Manthorpe R; Kofod B; Andreassen T; Oxlund H; Lorenzen I B
SO The Journal of rheumatology, (1976 Dec) Vol. 3, No. 4, pp. 367-74.
Journal code: 7501984. ISSN: 0315-162X.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197705
ED Entered STN: 13 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 25 May 1977
AB Thirteen patients, aged 27 to 70 years, with definite or classical rheumatoid arthritis were treated with penicillamine for six months. Skin biopsies and blood samples were compared with a clinical evaluation before and after therapy. The analyses of the skin included determinations of total collagen, thermal reaction of collagen, salt soluble collagen, in vitro uptake of 14C-proline and synthesis of 14C-hydroxyproline, as well as determinations of nucleic acids and proteoglycans. Serum concentrations of acute phase reactants, immunoglobulins, complement C3 and C4, rheumatoid factor, and iron, copper, and zinc were also determined. A positive correlation was found between clinical improvement and a fall in the number of granulocytes, a decrease in the concentration of acute phase reactants and serum copper, and an increase in salt soluble collagen of the skin. The total skin collagen decreased during treatment with penicillamine. The changes in skin collagen may reflect a generalized effect of penicillamine on collagen. These alterations may be part of an anti-inflammatory action of penicillamine.

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FULL ESTIMATED COST	9.33	9.54

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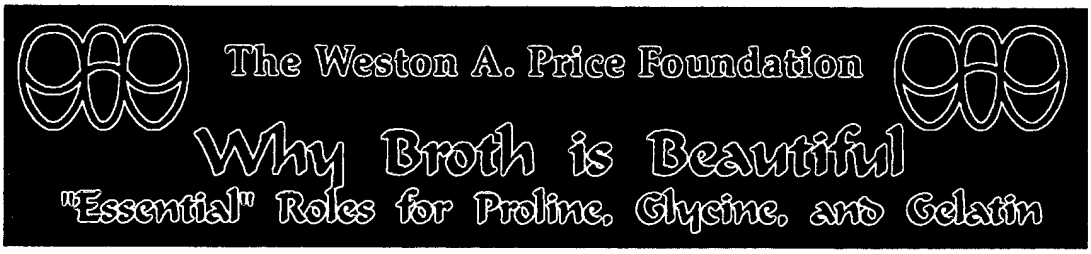

Why Broth is Beautiful--"Essential" Roles for Proline, Glycine and Gelatin

By Kaayla T. Daniel, MS CCN

Several years ago Knox Gelatin introduced a new product named Nutrajoint with great fanfare. This supplement contains gelatin, vitamin C and calcium, and advertisements touted "recent scientific studies" proving that gelatin can contribute to the building of strong cartilage and bones.

In fact, the evidence goes back more than a century, and not only established gelatin's value to cartilage and bones but also to the skin, digestive tract, immune system, heart and muscles.

These early studies, however, have fallen off the radar screen of Knox as well as that of nearly everyone else. So it was not surprising in 1997 when the editors of the *Tufts University Health & Nutrition Letter* advised consumers not to buy Nutrajoint or similar supplements because the idea that gelatin can contribute to the building of strong cartilage and bones "is a theory that has yet to be investigated." As for the theory itself, they sniffed that it "sounds tidy--rather along the lines of 'you are what you eat.'" In conclusion, they stated that even if Nutrajoint worked as claimed, it would be totally unnecessary because "the body can manufacture its own proline and glycine as needed and therefore suffers no shortfall."[1]

The notion that the body can create proline and glycine is, of course, the reason that neither amino is considered "essential."

The ability to manufacture them easily and abundantly as needed, however, is probably true only of people enjoying radiant good health.Common sense suggests that the millions of Americans suffering from stiff joints, skin diseases and other collagen, connective tissue and cartilage disorders might be suffering serious shortfalls of proline, glycine and other needed nutrients.

To understand why these nutrients might be so critical to joint health, I consulted several textbooks and learned that hyaline cartilage, the most common type in the human body, derives its strength from a dense, criss-crossing, ropey network of collagenous fibers, and its resilience from the gel-like matrix into which these fibers are embedded.

According to a textbook on bone disorders,[2] proline and glycine play starring roles in the collagenous fibers built from gigantic proteins containing some 1,000 amino acids each. Glycine contributes one-third of the total aminos. Glycine is a tiny amino with a talent for structuring very tightly packed chains. The other aminos that figure prominently are proline and hydroxyproline, an uncommon team with a passion for twisting themselves into tightly wound, left-handed helixes, then switching directions and twisting to the right into a superhelix. These little twisters form tight, tough, rodlike macro molecules, which in turn form thicker rods called fibrils. No wonder cartilage can have such impressive tensile strength.
The remarkable resilience of cartilage comes from its gelatinous matrix. Far from being a jiggling blob of all-natural Jello, this matrix is highly structured with complex proteins and sugars. Best known are the proteoglycans that wind over, under and around the collagenous fiber network. As the name suggests, these giant molecules are comprised of proteins and sugars. Their primary job is to get and hold water, and they were designed to be very, very thirsty. Accordingly, their elaborate structure includes a central strand of hyaluronic acid on which hang as many as 100 of the biggest proteins found in the body. These in turn, divide into chain gangs known as chondroitin sulfates and keratin sulfates. In electrical terms, these chains carry negative charges and so repel each other. By keeping their distance from each other, they create space for the very water they attract.

Living amidst the proteoglycans are the cartilage cells--chondrocytes--whose jobs are to regulate cartilage metabolism, manufacture the giant proteoglycan molecules and collagenous fibers and build new cartilage as necessary. To do so, the

chondrocytes need the right nutrients delivered in the right proportions by the water and synovial fluid that feeds cartilage. Not surprisingly, those nutrient needs include lots of the very aminos that collagen and cartilage are made of: proline and glycine. Although the textbooks don't come right out and say so--and the Tufts editors scorn the very concept--common sense suggests that--cartilage wise, at least--we might very well be "what we eat."

In fact there is solid scientific backing for this common sense observation. Research on proline and glycine is far from a growth industry, but a few good studies exist and serve to clarify the essential nature of these supposedly "inessential" aminos. Most of the researchers believe that both proline and glycine should at the very least be considered "conditionally essential" (along with arginine, cysteine, glutamine, serine, taurine and tyrosine)[3], which means that under most conditions, the body cannot make enough of these compounds and must get them from food. Even more interestingly, this modern research suggests that many of the long-forgotten 19th and early 20th century studies should be looked at anew.

Proline

Evidence is mounting that proline should be classified as an "essential" amino acid. Research shows that plasma levels fall by 20 to 30 percent when individuals in normal health are put on proline-free diets[4] This suggests that the body can produce proline but probably not in sufficient quantities without dietary assistance.

The Tufts editors thought proline deficiency highly unlikely because it is found in virtually all food proteins except lactalbumin, and because few Americans suffer malnutrition from starvation. However, people could still have low proline levels if they consume little protein. This is not only possible but probable in America today, given the popularity of high-carbohydrate, low-protein and low-fat diets. For most of these people the way to bring proline consumption up to par is obvious--add protein to the diet.

Occasionally, however, the problem is not protein intake but the body's inability to metabolize proline into the active form of hydroxyproline. Both acute and a chronic deficiency of vitamin C produce a significant increase in the proline to hydroxyproline ratio in urine,[5] a sign that the conversion is not being made.5 Iron is

another needed cofactor and vitamin C is well known to improve iron assimilation.[8, 9, 10, 11] Vitamin C's function is to maintain the enzyme prolyl hydroxylase in an active form: without this enzyme the proline and lysine in procollagen cannot be hydroxylated.[7]

As one might expect, proline has been recommended as a supplement that might benefit people interested in soft, non-sagging "youthful" skin. Little hard science backs up this idea, but a popular book by Leon Chaitow DO, ND recommends supplementation of 400-1000 mg per day and always along with Vitamin C. Chaitow cites research by Carl Pfeiffer discussed in *Mental and Elemental Nutrients* (Keats, 1975), but not apparently in journals.[12]

A study in the *Journal of Gerontology*, however, begged to differ, concluding that there were "no significant age-related variations in the content of proline, hydroxyproline, lysine and hydroxylysine over the range of 0-93 years of age." What they found was that "changes in cross-links derived from aldehyde may be responsible for the effects of age."[13]

Proline and Vitamin C also team up for other vital functions. Linus Pauling and Matthias Rath have proposed that heart patients with elevated lipoprotein (a) levels take a formula consisting of proline, lysine and vitamin C to help reverse the artery-blocking effects of lipoprotein (a).[14]

Glycine

Glycine might also be considered a "conditionally essential" amino acid.

As the simplest amino acid, it constitutes a basic nitrogen pool for manufacture of other amino acids, and it is used in the synthesis of hemoglobin, creatine, porphyrin, bile salts, glutathione and the nucleotides DNA and RNA. Glycine is involved in glucogenesis (the manufacture of glucose), and low levels may produce hypoglycemic-like symptoms.

Another vital function is detoxification. The human body requires copious amounts of glycine for detoxification after exposure to chemicals, and it conjugates directly with benzoic acid. In that individuals stressed with benzoic acid show inhibition of glutathione synthesis, and glycine is a precursor amino acid for

glutathione, some researchers have concluded that glycine might improve the functioning of Phase II hepatic detoxification. "Benzoic acid is used widely in the food industry as a preservative. Under normal circumstances these sources of benzoic acid can be handled with ease at the levels found in the total diet by most normal individuals. However, even these low levels might present a problem to individuals who already have a compromised glycine status in trying to satisfy an increased demand, such as pregnancy or sickle cell disease."[15]

Glycine also helps digestion by enhancing gastric acid secretion. Research published in 1976 established that only proteins stimulate gastric acid secretion, but apparently not all amino acids do so.[16] Glycine is one of those that do, a fact that was known in 1925.[17] The effects of other amino acids and their related peptides on acid secretion has not been determined, but researchers have proposed that "glycine may have application in the design of chemically defined diets for patients with gastrointestinal disorders."[18]

The ability to digest protein obviously plays a vital role in the maintenance of good health. Many popular health writers, including Adelle Davis and Linda Clark, have identified problems caused by widespread hydrochloric acid deficiencies, especially after the age of 40. As Davis put it, "Too little hydrochloric acid impairs protein digestion and vitamin C absorption, allows the B vitamins to be destroyed and prevents minerals from reaching the blood to the extent that anemia can develop and bones crumble." Strong words, but quite possibly backed by the wealth of studies she cites dating from 1939 to 1961.[19]

More recently, Robert Atkins, MD, has taken up the cry. "A lack of stomach acid is commonplace, the result of aging, genetics, use of certain medications and a variety of other factors." Citing 11 studies provided by his chief researcher Robert Crayhon, Dr. Atkins contends that the inability to properly digest protein contributes to asthma, diabetes, food allergies, osteoporosis, iron deficiency anemia, pernicious anemia, candida, rheumatoid arthritis, intestinal infections, psoriasis, vitiligo, hives, eczema, dermatitis, herpetiformis and acne."[20]

Glycine also plays a vital role in wound healing. In a study dating back to 1929, as well as more recent studies, evidence points to "a narrow margin between the metabolic demand for glycine and the

rate at which glycine can be formed or made available in the body. A marginal state of glycine availability is probably more common than has been appreciated in the past."[21] In other words, when the body needs glycine for repair, it probably cannot make all it needs, and must obtain additional glycine from the diet.

Researchers at Rutgers University also studied glycine and wound healing. Rats were fed diets with and without supplements of glycine plus arginine or glycine plus ornithine, and the team found that the glycine-plus-arginine combination significantly improved nitrogen retention in both the traumatized and non-traumatized rats. The researchers theorized that glycine and arginine were the most helpful because both "occur in particularly high concentrations in skin and connective tissue and might, therefore, be required in greater amounts for tissue repair." They further speculated that the beneficial effect of arginine-plus-glycine is "related to the creatine synthesis needed for wound healing."[22]

Yet another group of people likely to be short of glycine consists in patients with sickle cell anemia. "In sickle cell disease the ongoing haemolysis creates a demand for glycine of the order of 1-2 gram per day to satisfy the needs of haem synthesis. A normal dietary intake might just provide this amount of glycine, and endogenous synthesis of glycine must be insufficient to satisfy the remaining needs of the body. These people exist in a chronically precarious state with respect to glycine sufficiency."[23]

To meet so many and diverse metabolic demands, glycine must be readily available. The body can make it, obviously, but there are plenty of reasons to think that even normal, healthy people might not be able to make enough. For example, researchers found that the endogenous synthesis of glycine in adult men on low-protein diets failed to satisfy the normal metabolic demand. Studying both glycine and alanine, they found that glycine (but not alanine) synthesis declined when dietary amino acids were removed, especially at the lower intakes. Glycine metabolism (unlike alanine) appears to be "responsive to the amino acid composition of the diet." Although unsure of the exact metabolic and functional significance of this finding, they concluded that prolonged restriction of dietary nitrogen and/or the supply of glycine and dietary amino acids would probably limit the capacity of tissues to form creatine, prophyrins, purines and glutathione.[24]

Children and pregnant women also need goodly amounts of glycine in the diet. Research indicates that glycine deficiency could limit

growth in infants, and stated that the "demands of the growing fetus for glycine are very high, in both absolute terms and relative to other amino acids, two to ten times as great on a molar basis." By optimizing the intake of this amino acid, the outcome of pre-term infants could be improved.[25]

In addition, glycine is the limiting amino acid in children recovering from malnutrition, and it is the limiting amino acid for rapid growth.26 Furthermore, glycine status is an important marker of normal pregnancy. "As pregnancy advances the endogenous production of glycine may be insufficient to satisfy the increasing demands."[27]

Another infant feeding study showed that the sum of free amino acids in plasma increases after feeding and the ratio of glycine to valine falls. The type of meal determines how quickly this happens and how soon before normal levels are restored. Breast feeding as opposed to formula feeding produced faster alteration as well as speedier normalization.[28] This explains why prior to the mid 20th century, doctors recommended the addition of glycine-rich gelatin to the homemade infant formulas that were used when breast feeding was not possible.[29]

Taken together these studies strongly support the idea that if glycine is limited during the early months of life, growth could be limited as well. And once children grow up, the need for glycine does not diminish. As noted above, this little amino acid serves many metabolic functions and is not automatically produced in sufficient quantities by the body.

Gelatin: The Traditional Way to Ensure Adequate Proline and Glycine in the Diet

For many people the simple act of steering clear of low-protein diets and including sufficient protein might do the trick. Protein eaters who still come up short might choose to self medicate by taking proline and glycine supplements, but would be advised to order a custom-blended amino acid formula based on results of an amino acid assay test.

A better solution would be to improve their collagen status by adding gelatin to their diets in the form of gelatin-rich broth used in soups, stews and sauces. This traditional food, which has nearly disappeared from the American table, fits the "you are what you

eat" prescription to a T. Manufactured gelatin is also a useful item in that it is nothing less than heat-denatured collagen. However, because manufactured gelatin contains small amounts of MSG, it should be avoided by those who are sensitive to it.

Gelatin is especially rich in proline and hydroxyproline. According to a food industry website, it contains 15.5 and 13.3 grams per 100 grams of pure protein respectively. It also contains 27.2 grams of glycine per 100 grams pure protein. Lysine and hydroxoylysine needed for collagen synthesis are present in the smaller amounts of 4.4 and 0.8 grams per 100 grams pure protein. Others sources provide somewhat different figures (depending on the ingredients used in gelatin manufacture and the quality of their sources), but they all consistently show high levels of proline, hydroxyproline and glycine.

Gelatin, then, is rich in the proline and glycine components that people need, but weak in methionine, histidine and tyrosine and utterly lacking in tryptophan. Accordingly, textbook writers from the 19th century on have rated gelatin a "poor quality protein." But in spite of its seeming limitations, gelatin was valued for its medicinal benefits for thousands of years and was long considered a panacea for everything from skin and joint disorders to digestive distress to heart ailments.

Gelatin first began to fall out of favor in the 19th century when scientists demonstrated that a diet of bread and gelatin alone could not support life.30 The obvious conclusion--that gelatin is not a replacement for meat or other dietary protein--hardly means that it has no place at all in our diets. On the contrary, a substantial body of evidence exists suggesting that gelatin should have a very big place.

Unfortunately, most of these early studies are hard to locate, having been published in 19th century and early 20th century journals that are not found in most medical libraries. The two most valuable sources are a fascinating 1937 article by Francis Pottenger, MD, on the value of gelatin in digestion, and a copy of an obscure but very valuable 1945 book *Gelatin in Nutrition and Medicine* by N.R. Gotthoffer, Director of Research for Grayslake Gelatin Company, Grayslake, Illinois. In his foreword to this 162-page book, Gotthoffer states that he spent 18 years between 1927 and 1945 studying the scientific literature on gelatin.

Dr. Gotthoffer published his findings several years after Dr.

Pottenger announced his theories and research on the value of gelatin in health and digestion with great fanfare in 1937, at the Annual Meeting of the American Therapeutic Society in Atlantic City. "Gelatin may be used in conjunction with almost any diet that the clinician feels is indicated," said Pottenger. "Its colloidal properties aid the digestion of any foods which cause the patient to suffer from 'sour stomach.' Even foods to which individuals may be definitely sensitive, as proven by the leucopenic index and elimination diets, frequently may be tolerated with slight discomfort or none at all if gelatin is made part of the diet."[31]

By then, Dr. Gotthoffer had already turned up many earlier studies supporting gelatin's role in digestion. Early in this century researchers showed that gelatin increases the utilization of the protein in wheat, oats, and barley, though not of corn; that the digestibility of beans is vastly improved with the addition of gelatin; and that gelatin helps the digestion of meat protein.[32] The last appears to confirm the subjective reports of many people who say that meats found in soups and pot roasts--cooked with bones for a long time in a liquid to which a touch of vinegar has been added--are easier to digest than quickly cooked steaks and chops, and why gelatin-rich gravies are at the heart of many culinary traditions.

Confirming recent studies showing that glycine helps infants grow properly, Gotthoffer reports the existence of more than 30 years of research studies showing that gelatin can improve the digestion of milk and milk products. Accordingly, nutrition textbook writers of the 1920s and 1930s recommended that gelatin be included in infant formulas to help bring cow's milk closer to human milk. Gotthoffer's explanation was that the "curd obtained from the coagulation of woman's milk was softer and more easily digested than that of cow's milk. However, when gelatin was added to cow's milk, a curd of equally desirable characteristics was formed. In addition, gelatin exerted a very important influence on the milk fat. It served not only to emulsify the fat but also, by stabilizing the casein, improved the digestibility and absorption of the fat, which otherwise would be carried down with casein in a lumpy mass." As a result, infants fed gelatin-enriched formulas showed reduced allergic symptoms, vomiting, colic, diarrhea, constipation and respiratory ailments than those on straight cow's milk.[33]

Likewise Gotthoffer found studies showing that convalesing adults who have lost weight because of operations, dysentery, cancer and other illnesses fare better if gelatin is added to their diet. "It is said

to be retained by the most sensitive stomach and will nourish when almost nothing else will be tolerated," wrote L. E. Hogan in 1909.[34] One reason gelatin was recommended so highly for malnourished individuals was that it diminishes the amount of complete protein needed by the body.

The "sparing" effects of gelatin on protein were of particular interest to many early researchers. By "sparing protein," they meant that the body is less likely to cannabilize the protein stored in its own muscles, a common occurrence during fasting or during rapid weight loss from illness. Gelatin thus helps keep the body in what today's nutritionists call "nitrogen balance." As Carl Voit, a researcher who spent ten years studying gelatin, wrote in 1872, "By being itself decomposed, it prevented the breakdown of protein in the body and thus exerted its remarkable sparing powers." He found that gelatin alone, however, was not able to build up protein supplies in the body.[35]

Gelatin and Digestion

Voit also found that gelatin improved digestion because of its ability to normalize cases of both hydrochloric acid deficiencies and excesses, and was said to belong in the class of "peptogenic" substances that favor the flow of gastric juices, thus promoting digestion.[36]

Gelatin's traditional reputation as a health restorer has hinged primarily on its ability to soothe the GI tract. "Gelatin lines the mucous membrane of the intestinal tract and guards against further injurious action on the part of the ingesta," wrote Erich Cohn of the Medical Polyclinic of the University of Bonn back in 1905. Cohn recommended gelatin to people with "intestinal catarrh"--an inflammation of the mucus membrane now called irritable bowel syndrome. Interestingly, the type of gelatin used in follow-up experiments done on people with even more serious intestinal diseases was specified as a "concentrated calves foot broth."[37] This form of gelatin would have been rich in cartilage and bone and presumably provide a better amino acid profile than straight collagen.

Today clinical nutritionists see more and more cases of dysbiosis--imbalances of "good" and "bad" bacteria in the intestinal tract. In that the fermentative disturbances that result are linked to allergies to grains and/or excessive carbohydrate consumption, it

is fascinating to find that a researcher named C.A. Herter spoke directly to that point back in 1908:

"The use of gelatin as a foodstuff in bacterial infections of the intestinal tract has never received the attention it deserves. The physician is not infrequently confronted with a dietetic problem which consists in endeavoring to maintain nutrition under conditions where no combination of the ordinary proteins with fats and carbohydrates suffices to maintain a fair state of nutrition. The difficulty which most frequently arises is that every attempt to use carbohydrate food is followed by fermentative disturbances of an acute or subacute nature which delay recovery or even favor an existing infection to the point of threatening life. A great desideratum, therefore, is a food which, while readily undergoing absorption, shall furnish a supply of caloric energy and which at the same time shall be exempt from ordinary fermentative decomposition. Such a food exists in gelatin."[38]

Years later Schwick and Heide found that excess hydroxyproline-containing proteins in serum and urine provides a reliable marker of pathological conditions. They posited that the breakdown of collagen most probably results from an antigenic reaction. "Not so long ago the opinion prevailed that gelatin was not antigenic or immunogenic. However, with the introduction of sensitive immunological methods -- particularly the haemagglutination techniques --antibodies against gelatin could be demonstrated. It was surprising to find antibodies against gelatin in human and animal serum of individuals who had never been injected with gelatin or collagen." Schwick and Heide added that this occurs frequently in cases of rheumatoid arthritis and other degenerative joint diseases. [39]

Though they offered no explanation for this pathological occurrence, many clinical nutritionists report that rheumatoid arthritis and degenerative joint diseases reverse when priority is given to the healing of the GI tract and of "leaky gut" syndrome (in which incompletely broken down proteins cross the mucosal barrier and enter the bloodstream and tissues only to be attacked by the immune system). Because healing protocols generally involve the avoidance of antigenic foods, Schwick and Heide's findings might lead some readers to put gelatin on their already long list of foods to avoid.

However, gelatin is precisely what the turn-of -the-century doctors ordered, not only to heal digestive disorders and the intestinal

mucosa but all allergies. Gelatin was even sometimes injected as a plasma or blood substitute.40 More recently, John F. Prudden, MD, DSci discovered that therapeutic doses of cartilage (which always contains copious amounts of proline and glycine) dramatically improved rheumatoid arthritis as well as other degenerative joint conditions and inflammatory bowel diseases.[41]

Additional evidence comes to us recently from a team of Russian researchers. In an article in *Pathophysiology*, they reported that gelatin will protect gastric mucosal integrity, at least in lab rats subjected to ethanol-induced mucosal damages.[42]

Doctors of the past also once knew the value of gelatin in treating celiac disease. In 1924, a researcher named Haas stated that the response of patients to a low-carbohydrate diet in which gelatin "milks" were given at the noon and evening meals was "striking and almost uniformly good results were obtained over a period of about ten years."[43]

Today many people have solved their digestive problems by following the food combining rules popularized in the bestseller *Fit for Life* by Harvey and Marilyn Diamond (Warner, 1985), which was inspired by the work of natural hygiene pioneer Herbert Shelton. Particularly pertinent here is the rule that warns us never to eat protein foods with starches. The reason is that they are supposedly digested on different timetables in the gut, upping the likelihood of indigestion.
Dr. Pottenger, however, found that if gelatin is included as part of the meal, digestive action is distributed throughout the mass of food and digestion of all components proceeds smoothly.[44]

A more recent theory that has helped many people's digestion is laid out in the book Eat Right 4 Your Type by Peter J. D'Adamo (Putnam, 1996). Yet the very grains that Dr. D'Adamo has found to be a problem for people with Type O bloods are easily digested if soaked, then cooked in a gelatin-rich broth. Type A people--who typically lack the abundant secretions of hydrochloric acid (HCl) necessary for easy digestion of meats--find meats far easier to digest if they are served with a gelatin-based gravy, cooked in a gelatin broth or served after drinking a cup of properly made soup and, as we have seen, gelatin may even increase their production of HCl. Finally gelatin can alleviate the allergic reactions and sensitivities that Dr. D'Adamo has related to blood Types B and AB. Thus gelatin not only opens up the dietary possibilities for each blood type but can prove a boon for married couples of

different blood types who would obviously prefer to eat the same meals.[45]

Fifty years ago Pottenger pointed out a reason that raw food diets can be so effective in reversing disease and contributing to rejuvenation. "Man's food in the raw state consists largely of hydrophilic (water loving) colloids. The heat of cooking on the other hand . . . precipitates the colloids of our diet. This change in colloidal state alters the hydration capacity of our foods so as to interfere with their ability to absorb digestive juices." Happily for those who prefer their food cooked, Dr. Pottenger went on to explain that this digestive problem could be easily remedied by adding one-half ounce to one ounce of gelatin to a cooked meal of meat, potatoes, vegetables and fruits. [46]

Edgar Cayce--the "Sleeping Prophet" whose extraordinary psychic readings have often anticipated modern medical science by decades--also had good things to say about gelatin and digestion. In his readings he recommended that gelatin be consumed to help the assimilation of vitamins, help the glands function better and to optimize energy and health. Particularly relevant was Cayce's counsel that raw vegetables and salads be eaten with gelatin.[47]

Gelatin and the Liver

Early research has also indicated that gelatin helps the liver. This is plausible in that the liver uses the amino acid glycine for detoxification, and its ability to detoxify is limited by the amount of glycine available. Back in 1935, Reuben Ottenberg, MD wrote in the *Journal of the American Medical Association*: "It has been suggested that the administration of extra amounts of proteins containing an abundance of glycine (such as gelatin) will help the work in the liver. This seems particularly plausible since the recent work of Quick, who has shown that the ability of the liver to perform this protective synthesis is limited by the amount of glycine available."

Ottenberg concluded with the recommendation that patients with jaundice and other liver problems take 5 to 10 grams of gelatin per day either in the form of food or as a powdered medicinal supplement.[48]

Gelatin and Bone Health

Interestingly enough, Gotthoffer didn't find a lot of studies supporting the role of gelatin in joint and bone health, though a 1907 Italian study established that gelatin injections increased the calcium in the circulating blood, which in turn was shown to stimulate bone building.[49]

Recent studies, however, do support such use. A Japanese study reported on protein undernutrition, lowered bone mass and osteoporotic fracture. Mice were fed for ten weeks with a low-protein diet containing either 10 percent casein or a combination of 6 percent casein and 4 percent gelatin. The bone mineral content and bone mineral density of the femur were significantly higher in the group given 6 percent casein plus 4 percent gelatin. The researchers concluded, "these results suggest that gelatin has differential effects on bone mineral density and body weight in protein undernutrition."[50]

A 1999 German study also proved the truth of the saying "*Man ist was man isst*." Their study was inspired by reports of the positive influence of gelatin on degenerative diseases of the musculo-skeletal system and curiosity about the "therapeutic mechanism and the absorption dynamics." Mice fed radioactive gelatin hydrolysate were compared to control mice administered radioactive proline. They found that 95 percent of the gelatin was absorbed within the first 12 hours, and the labeled gelatin found in the tissues was similar to that of labeled proline with one exception--the absorption and accumulation of gelatin in the cartilage was twice as high. This suggested a salutary effect of gelatin on cartilage metabolism that would not occur with the ingestion of proline alone. They concluded, "These results demonstrate intestinal absorption and cartilage tissue accumulation of gelatin hydrolysate and suggest a potential mechanism for previously observed clinical benefits of orally administed gelatin."[51]

In 2000, Dr. Roland W. Moskowitz of Case Reserve University published the results of his review of the literature on collagen hydrolysate in the treatment of osteoporosis and osteoarthritis. He was particularly impressed with clinical studies that suggested that 10 grams of pharmaceutical grade collagen hydrolysate per day were enough to reduce pain in patients with osteoarthrisis of the knee or hip and that gelatin held a significant treatment advantage over the placebo. For bone patients, Moskowitz concluded that studies of the effects of calcitonin (a hormone known to participate in calcium and phosphorus metabolism with and without a

collagen-hydrolysate-rich diet showed that calcitonin plus the gelatin inhibited bone collagen breakdown far better than calcitonin alone.[52]

The big question is why so many early studies showing the healing power of gelatin have languished in obscurity. The easy explanation is that after the 1930s, pharmaceutical drugs were widely prescribed for ills that were once healed with gelatin.

A more complete explanation is that many of the results of the early studies could not be replicated. Reading Gotthoffer's compendium, it is evident that one scientist would find that gelatin helps prevent, say, muscular fatigue, the next would find some benefit and a third would see no benefit at all. And so on with anemia, jaundice, ulcers and other ailments. Not being able to repeat and verify results, scientists probably moved on to other substances and apparently never found the key to why gelatin sometimes worked well and sometimes did not.

Why were the studies so variable in their results? The most probable explanation is that the substance described as "gelatin" was not consistent from study to study.

Most commercial gelatins today are brewed exclusively from pigskins or cowhide and so include no cartilage or bones. Years ago, however, some commercial cartilages came from mystery blends of cartilage, bones, skin and other junked animal parts. All these combinations differed in terms of their physical and chemical characteristics and in their physiologic actions. Gotthoffer reported that even glue was sometimes sold as gelatin. Complicating matters further, some of the so-called "gelatin" studies were done with the isolated amino acid glycine.[53]

Given the inconsistencies and hazards of gelatin manufacture, it is no wonder that studies were inconsistent. As for using gelatin today for therapeutic benefits, the highest quality product would come from making gelatin at home using skins, cartilage and bones from organic chicken or meat. As Dr. Pottenger was wont to say: "A big stock pot is the most important gift a bride could receive."[54]

Whatever form of gelatin is used, it should never be cooked or reheated in the microwave. According to a letter published in *The Lancet*, the common practice of microwaving converts l-proline to d-proline. They write, "The conversion of *trans* to *cis* forms could

be hazardous because when *cis*-amino acids are incorporated into peptides and proteins instead of their *trans* isomers, this can lead to structural, functional and immunological changes." They further note that "d-proline is neurotoxic and we have reported nephrotoxic and heptatotoxic effects of this compound."[55] In other words, the gelatin in homemade broth confers wonderous benefits, but if you heat it in the microwave, it becomes toxic to the liver, kidneys and nervous system.

Another study suggested that the l-configuration and the proper molecular size are both essential for beneficial effects of l-proline upon memory and for the prevention of depression. [56] There is no reason to think that proline is the only amino subject to this kind of destruction, and it is likely that other aminos would be similarly affected. The studies, however, were done on proline.

Concerned about possible excesses of the amino acids proline and glycine? Humans have shown a high tolerance for both proline and glycine with no ill effects. When people develop problems attributed to an excess of proline, it is the result of a genetic disorder, not the result of food or supplementation. In those few cases excess proline causes renal and central nervous system dysfunction.[57] Glycine excess also can be attributed to a genetic disorder and indicates a very rare genetic metabolism problem that can manifest as severe mental retardation. Although this occurs very rarely, it should be evaluated in any individual who is going to supplement with large doses in pill form.[58]

Not By Gelatin Alone

Historically, gelatin ingestion has caused health problems but nearly all the documented cases occurred when the subjects were fed excessive amounts of gelatin and little else. This occurred quite frequently during the early to mid 19th century when people running hospitals, soup kitchens and poor houses tried to economize by serving gelatin at every meal in the form of bouillon, gelatinous biscuits and other gelatin-based edibles--or inedibles as the case may be. Gelatin bashers have long been fond of quoting one scientific study in which dogs died after a few weeks on a gelatin diet. While it was true that the dogs died, Gotthoffer argued that "no account was taken of the fact that the animals refused to eat the food after a few days."[59]

Remember also that the amino acids in gelatin, like all amino

acids, can only be properly utilized when the diet contains sufficient fat-soluble activators--vitamins A and D--found exclusively in animal fats. So don't hesitate to put cream in your broth-based soups and sauces, and include other sources of vitamins A and D in your diet, such as butter, egg yolks and cod liver oil.

These days no one is worried about eating too much gelatin, though a lot of people are worried about eating any gelatin at all. The fear is "Mad Cow" disease. An industry website (it does not reveal its sponsor) states that gelatin today is "hide gelatin," never made from brains, and that processing procedures such as degreasing, acid demineralization, alkaline purification, washing, filtration, ion exchange and sterilization reduce the chance of bovine spongiform encephalopathy to less than zero.[60] Whether this is honest information or a public relations spin, or a little bit of both, is not known, and research into this subject is outside the scope of this paper. In 1992, the FDA took the fear seriously enough to forbid the import of any cow products including gelatin from countries where BSE occurs, but lifted the ban on gelatin in 1997. The main reason was that there have been no cases to date implicating either commercial or homemade gelatin in "Mad Cow" disease or any other neurological disorders.[61]

In favor of gelatin are thousands of years of historical reports and several hundred years of studies, most of which suggest that gelatin-rich broth is the key to turning a quivering blob of ill health into a sturdy specimen of good health. As the South American proverb puts it, "Good broth can resurrect the dead."[62]

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Better Than Pills and Potions - Broth

Many studies now confirm what Grandma always knew--that broth made from bones is a great remedy, a tonic for the sick, a strengthener for athletes, a digestive aid, a healing elixir. And unlike bitter medicines, broth can be incorporated into delicious soups, stews and sauces. In fact, broth is the basis of all gourmet cuisines. "Without broth," said Escoffier, "one can do nothing."

The basic method is simple. Soak bones (chicken, duck, turkey, beef, lamb, fish, etc.) in water plus a little vinegar for an hour or two. If you are using beef or lamb bones, a better color and flavor will result by first roasting the bones in the oven. Bring the water to a boil slowly and skim any scum that rises to the top. Add a variety of vegetables and herbs and allow to simmer several hours or overnight. Remove the bones (your dog will love them) and strain out the vegetables. You can use the stock as is, or chill to remove the fat that congeals on the top. (There is nothing wrong with the fat, but culinary purists point out the clearest sauces are achieved with stock from which the fat has been removed.) The stock may be kept in the refrigerator for several days or in the freezer for several months.

If you have a large enough pot, you can use whole carcasses of birds or fish, and large knuckle bones (full of cartilage) of beef. Our local supplier of farm products prepares broth in a cauldron large enough for the cow's head--the result is a fantastic, gelatinous broth.

The substitute for broth is MSG, which food manufacturers use to achieve the taste of meat in canned and dehydrated soups and in imitation sauces. MSG is toxic to the nervous system but broth--rich in calcium--is protective. One of the most important things you can do to improve your health is to use real broth and avoid imitation foods.

A Recipe for Strong Cartilage, Limber Joints and Beautiful Skin

From our friends in Australia promoting the "Optimal Diet," developed by Polish doctor Jan Kwasniewski, comes this recipe for joint and cartilage health, as well as for beautiful skin. Boil a piece of pig skin for at least 3 hours until it becomes very soft. Eat it as is, with mustard or horseradish, or put it through a mincer and add it to other food. The important thing is regular use--a tablespoon or more every day, along with a diet that contains adequate animal protein and lots of nourishing animal fats.

Connective tissue is regenerated very slowly, so this is a remedy that requires some patience. However amazing results have been reported--healing of joints that had been completely stiff and frozen and the gradual disappearance of arthritis. Best of all is the improvement in skin quality, with wrinkles smoothing out and even disappearing completely.

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